REMARKS

Upon entry of this amendment, claims 3, 23, 49, 50-70, and 76-81 will be pending and under consideration. Claims 71-75 were submitted in the response to the final Office Action before filing the Notice of Appeal, but these claims were not entered by the Examiner according to the Advisory Action mailed on November 22, 2002. Applicants respectfully request reconsideration in view of the following remarks. In addition, it is Applicants' understanding, based on a March 21, 2003 telephone conference between the Examiner and the undersigned, that claim 76 and its dependent claims are allowable. Issues raised by the Examiner will be addressed below in the order they appear in the prior Office Action.

Applicants note that the Examiner has acknowledged the acceptance of the drawings filed on June 6, 2002.

Claim rejections under 35 U.S.C. 112, first paragraph

Claims 3, 23 and 49-75 stand rejected under 35 U.S.C. 112, first paragraph, as allegedly lacking enablement and as allegedly failing to provide an adequate written description of the invention in the specification.

In particular, regarding the written description requirement, the Office Action has objected to the phrase "an agent that stimulates *in vivo* a therapeutically effective concentration of an endogenous morphogen", since only a method for screening and isolating the particular agents, rather than the agents themselves, is described in the specification. Furthermore, the Office Action asserts that a single type of protein (morphogen) is not representative of the class of "agents" recited in the claims.

Applicants have amended claims 3, 23, and 49, and added new dependent claims 77-81 to obviate this rejection. Support for these amendments can be found throughout the specification, for example, see Example 15. Amended method claims 3, 23, and 49 now include a step (i) to first identify an agent that stimulates *in vivo* a therapeutically effective concentration of an endogenous morphogen, and a step (ii) to administer one or more agents identified in step (i), so that the increased morphogen levels *in vivo* help to achieve the stated goals recited in the

preambles. Applicants contend that these amendments obviate the above rejection and respectfully request that the Examiner reconsider and withdraw this ground of rejection.

In addition, Applicants have added new independent claim 76 and its dependent claims 77, and 79-81 to further clarify the subject matter claimed.

Regarding the enablement requirement, Applicants submit that the amended claims are enabled throughout their scope.

The Office Action asserts that the assay of Example 15 is for identification of agents that increase morphogen production by a cell in culture, which are not accepted model systems for the diseases recited in the claims, nor are the morphogen levels produced by the cells tested for "therapeutically effective concentrations" as required by the claims.

To enable the claimed methods, Applicants submit that the disclosed cell culture system for identifying the agents need not correlate to model systems for the diseases recited in the claims. This is not because a reasonable correlation between data generated *in vitro* to the claimed particular therapeutic or pharmacological method is not required, but because any agents that can stimulate morphogen production *in vitro* in a tissue culture system can be reasonably expected to stimulate morphogen production *in vivo*, at least in the same cell types that are originally tested *in vitro*. Since morphogens are secreted from cells producing morphogens, and the instant specification teaches that biologically active morphogens are naturally present in several body fluids, such as blood / serum, saliva, milk, etc. (see page 62, first paragraph of Example 2), it can be reasonably concluded that an agent that stimulates morphogen production locally (e.g., from one or more particular sites, including from multiple different local tissues known to be able to express morphogens, as described by Example 1) will lead to a systemic elevation of morphogen level *in vivo*, which in turn can reach tissues normally that do not express morphogen themselves, but nevertheless can benefit from morphogen-dependent therapeutic effects. This proposition is further supported by several experiments disclosed in the specification (see for example, Examples 3 and 4), wherein morphogens are administered intravenously to treatment group animals, which clearly show improved recovery from various

tissue injuries when compared with control group animals. Therefore, the ability of an agent to stimulate morphogen production *in vitro* in a given cell (for example, a lung cell), can be reasonably correlated with the agent's ability to stimulate morphogen production *in vivo*, at least in the same cell-type (e.g., lung cell); and that the secreted morphogen will be systemically delivered to other tissues (such as skin, etc.) via body fluids such as blood, and provide morphogen-dependent benefits to such other tissues.

Regarding whether the morphogen levels produced by the cells are tested for "therapeutically effective concentrations," Applicants submit that such tests are not required for enabling the claimed invention. Pursuant to MPEP 2173.05(c), "[t]he more recent cases have tended to accept a limitation such as 'an effective amount' as being definite when read in light of the supporting disclosure and in the absence of any prior art which would give rise to uncertainty about the scope of the claim. In *Ex parte Skuballa*, 12 USPQ2d 1570 (Bd. Pat. App. & Inter. 1989), the Board held that a pharmaceutical composition claim which recited an 'effective amount of a compound of claim 1' without stating the function to be achieved was definite, particularly when read in light of the supporting disclosure which provided guidelines as to the intended utilities and how the uses could be effected." (emphasis added). The instant specification meets both of these criteria. Since what constitutes a "therapeutically effective amount" depends on a number of factors, such as those listed in the paragraph bridging pages 56-57 of the specification, the question is best answered by a skilled artisan (such as an attending physician) depending on specific uses. If the exact amount of morphogen to be used can be unspecified for a particular use without affecting enablement, it follows that there is no need to test if an identified agent will stimulate the production of an as-yet unspecified amount of morphogen. In addition, a skilled artisan (physician) would be able to gradually increase the level of induction (for example by increasing the dosage of the inducing agents) of morphogen expression until a sufficient quantity of morphogens are synthesized to provide the desired effect.

The Office Action also asserts that Laufer, Hogan, and Roberts cannot be used to enable the claimed invention. Without acquiescing in the arguments of the Office Action, Applicants submit that amendments to claims 3, 23, and 49 have rendered these arguments moot. The amended claims do not depend on an allegedly unidentified agent. Rather, a skilled artisan can practice the claimed methods by first identifying an agent according to the teaching of the

specification, and then administering the identified agent(s) to the intended subject (e.g., human). Since there is no rejection on grounds of enablement to the step corresponding to current step (ii) in any previous Office Actions, to argue that the amended claims are not enabled, evidence would have to be provided to show why a skilled artisan, in view of the specification, would not be able to identify a subject agent in step (i). In theory, if a single agent of desired effect can be identified according to step (i), no matter how inefficient or unsuccessful the actual processes are, the amended claims are enabled. In fact, Applicants submit a recent article by Bouletreau *et al.* (Plast Reconstr Surg 109(7): 2384-97, June 2002, abstract submitted as **Exhibit A**), which demonstrates that vascular endothelial growth factor (VEGF) can stimulate the expression of BMP-2 mRNA and protein in endothelial cells in endothelium, which, according to the authors, is "a metabolically active secretory tissue, capable of responding to a wide array of environmental stimuli." Since blood vessels comprise endothelial cells, VEGF delivered intravenously will stimulate morphogen production in endothelial cells, and the secreted morphogen in turn is expected to reach most other tissues that have access to the cardiovascular system.

In addition, Applicants submit that the mere absence of a working example in the specification (an identified agent according to step (i)) is not by itself evidence that the claimed invention is non-enabled. Substantial scientific evidence developed since the filing of the instant application has *confirmed* that such agents do exist, as the instant application teaches. A skilled artisan would be reasonably expected to identify at least a few of these agents by conducting a routine screen assay based on the teaching of the specification. Applicants do not rely on any of these later scientific publications for enablement, since they add nothing more to the claimed methods than what is already taught. Rather, these scientific publication merely serve as evidence that the claimed invention can and will work if the teachings of the specification are followed.

Nor is the amount of the experiment undue. Applicants submit that a screen of a large amount of candidate compounds for agents of certain desired activity is merely routine drug discovery protocol, where millions, if not hundreds of millions, of compounds are routinely obtained and screened, typically over a long period of time and through a large investment of labor and capital Thus, such a screen does not constitute undue experimentation. Neither does a

high rate of failure or low predictability of success alone make the experimentation "undue." To support these views, Applicants wish to draw the Examiner's attention to several controlling cases regarding what type and amount of experimentation is reasonable rather than undue.

In *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 231 USPQ 81 (Fed. Cir. 1986), CAFC rules that "the trial court erred in finding a lack of enablement for failure to set forth the methods of making monoclonal antibodies and of screening for proper antibodies. The evidence indicated that both methods were known to person skilled in the art." Therefore, simply setting forth a screening method to obtain a substance (monoclonal antibody / agent / "substance") with a desired function (binding a specific antigen, etc.), even though the well-known methods (making and screening for monoclonal antibody) are not explicitly disclosed in the application, is enabling for those substances that are not yet obtained, but nevertheless can be obtained if the methods taught by the specification are followed. Since "the specification need not disclose what is well-known to those skilled in the art and preferably omits that which is well-known to those skilled and already available to the public. *In re Buchner*, 929 F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991)." (MPEP 2164.05(a)).

Neither does the screening method need to be a *foolproof* one. In other words, the taught method need not be one that will guarantee a high rate of success. In *Johns Hopkins University v. Cellpro., Inc.*, 152 F.3d 1342, 47 USPQ2d 1705 (Fed. Cir. 1998), the patentee claimed a genus of monoclonal antibodies specific for a weak antigen CD34, while showing only one working monoclonal antibody. The accused infringer argued that the patentee did not enable a skilled artisan to make any antibodies other than the one shown. The CAFC ruled that the claim in question was enabled, even though the laboratory of one of the named inventors failed to produce a second antibody falling within the scope of the claimed invention after a "major effort." The Court states that "[I]t is imperative when attempting to prove lack of enablement to show that one of ordinary skill in the art would be unable to make the claimed invention without undue experimentation." Regarding what constitutes undue experimentation, there are two sources that could contribute to the amount of experimentation. One source arises from the intrinsic nature of the problem to be solved, in that case, to obtain a monoclonal antibody specific for an intrinsically weak antigen CD34. Indeed, one expert witness of the infringer testified that it was generally "more difficult" for him to produce a CD34 antibody than other

monoclonal antibodies, and he attributed this difficulty to the weak immunogenicity of the source antigen. The other source derives from situations wherein the patent disclosure is insufficient so that a skilled artisan could not, even when properly following the guidance of the specification, make and use the claimed invention, thus leading to undue experimentation by the skilled artisan. The Court ruled that since the expert "explained that the relative difficulty that was encountered in producing CD34 antibodies may have been due to the weak immunogenicity of the KG-1a cell line, ... not because of an insufficiently enabling disclosure," this "suggests that the Kohler/milstein technique was not foolproof, and that success with this technique commonly required repetition. This lack of certainty was thus not attributable to a failure of disclosure in the '204 patent" (emphasis added). Clearly, the amount of experimentation is only undue if the skilled artisan has to engage in experimentation to compensate for "an insufficiently enabling disclosure," but not when the specification has disclosed everything a skilled artisan needs to know to carry out the experiment, even if the amount of such experiment is routinely large.

Similarly, Applicants submit that the instant specification discloses a screening method that can be used to obtain agents capable of stimulating morphogen production, just like a skilled artisan would have been able to obtain the CD34 antibody if he followed the disclosure of the '204 patent above. The screening process may even be tedious and have an unpredictable success rate due to the nature of the problem, just like the screen for a CD34 antibody. But since morphogens typically exhibit tissue-specific distribution, this phenomenon inherently teaches that morphogen expression *in vivo* is tightly regulated by the surrounding environment of different tissues. There must be agents, either natural or synthetic, that are capable of regulating the expression of morphogens *in vivo*. Therefore, a skilled artisan would have been able to identify such substances through routine experimentation using the taught method. To rebut this argument, it would have to be shown why one of ordinary skill in the art would have been unable to make the claimed invention without undue experimentation, and that the amount of experimentation is due to insufficient disclosure of the specification rather than the nature of the problem to be solved.

Based on the above arguments, Applicants submit that all amended claims satisfy all of the requirements of 35 U.S.C. 112, first paragraph. Therefore, reconsideration and withdrawal of this rejection are respectfully requested.

New Matter Rejection

Claims 50-70 were rejected under 35 U.S.C. 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the invention(s), at the time the application was filed, had possession of the claimed invention. The Office Action asserts that this is a new matter rejection.

Applicants submit that the claimed invention relates to methods of identifying agents that stimulate the in vivo production of morphogens, and using such identified agents to treat certain diseases. The paragraph bridging pages 9-10 provides explicit support for the claimed invention. The paragraph explicitly describes the use of the claimed invention to protect "tissues and organs from the tissue distructive effects of the inflammatory response." (emphasis added) Thus, a skilled artisan would readily recognize that the claimed invention would be suitable to treat all disease conditions associated with inflammatory responses, especially those described explicitly in other sections of the specification, such as the ones recited in claims 50-70.

Pursuant to MPEP 2163.02 (8th edition released in August, 2001) "An objective standard for determining compliance with the written description requirement is, 'does the description clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed.'"

In view of the guidelines above and the arguments presented, Applicants respectfully submit that claims 50-70 are properly supported by the instant specification. Reconsideration and withdrawal of the rejection is respectfully requested.

CONCLUSION

In view of the foregoing amendments and remarks, Applicants submit that the pending claims are in condition for allowance. Early and favorable reconsideration is respectfully solicited. The Examiner may address any questions raised by this submission to the undersigned at 617-951-7000. Should an extension of time be required, Applicants hereby petition for same and request that the extension fee and any other fee required for timely consideration of this submission be charged to **Deposit Account No. 18-1945.**

Respectfully Submitted,

Date: August 28, 2003

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1: Plast Reconstr Surg. 2002 Jun;109(7):2384-97.

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Hypoxia and VEGF up-regulate BMP-2 mRNA and protein expression in microvascular endothelial cells: implications for fracture healing.

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The endothelium is a metabolically active secretory tissue, capable of responding to a wide array of environmental stimuli. Hypoxia and vascular endothelial growth factor (VEGF) are two components of the putative fracture microenvironment. This study investigated the role of hypoxia and VEGF on endothelial cell activation as it relates to the bone repair process. It was hypothesized that endothelial cells may have an important osteogenic role in fracture healing through the production of bone morphogenetic protein-2 (BMP-2), an osteogenic cytokine at the fracture site. Therefore, BMP-2 mRNA and protein expression in endothelial cells under hypoxia and/or VEGF treatment was studied. The authors observed a 2-fold to 3-fold up-regulation of BMP-2 mRNA expression in bovine capillary endothelial cells and human microvascular endothelial cells stimulated with hypoxia or rhVEGF. Furthermore, the combined effects of hypoxia and rhVEGF appeared to be additive on BMP-2 mRNA expression in bovine capillary endothelial cells. Actinomycin D and cycloheximide studies suggested that the increased mRNA expression was transcriptionally regulated. BMP-2 protein expression was up-regulated after 24 and 48 hours of treatment with either hypoxia or rhVEGF in bovine capillary endothelial cells. Surprisingly, the data suggest that endothelial cells may play not only an angiogenic role but also an osteogenic role by a direct stimulation of the osteoblasts, through the enhanced expression of a potent osteogenic factor, BMP-2, at the fracture site.

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